LETTERS TO THE EDITOR

Abnormal circadian rhythms of plasma melatonin and body temperature in the delayed sleep phase syndrome

In a study published in this *Journal* in 1992 Alvarez *et al* described normal profiles of plasma melatonin in a group of 12 patients with the delayed sleep phase syndrome, an idiopathic sleep disorder manifested by an inability to fall asleep and wake spontaneously at desired clock times and a phase delay of the major sleep episode in relation to the desired time for sleep.[1] Because of animal data indicating a central role of melatonin in circadian regulation, they obtained 24 hour plasma melatonin profiles of patients with delayed sleep phase syndrome in a fixed light-dark ward environment (dark period 2300–0800). On average, plasma melatonin concentrations peaked about 0400 and reflected a normal adult pattern of melatonin secretion. Intrinsic patterns of human melatonin secretion, however, may be masked by patterns of sleep and light exposure.[2] Evaluation of circadian oscillator rhythms are best unmasked in "constant routine" periods of at least 24 hours of virtual darkness that are designed to minimise or distribute evenly the possible "masking effects" of sleep, posture, exercise, meals, and light, which might distort the intrinsic patterns of circadian rhythms.[3] Therefore, we evaluated circadian plasma melatonin concentrations and core body temperature with a 24 hour dark (<1 lux) period constant routine in a patient with the delayed sleep phase syndrome

A 43 year old woman presented to our clinic with a 30 year history of the delayed sleep phase syndrome, primarily manifest by an inability to fall asleep before 0400 and a difficulty in waking before 1200 daily. Although brain MRI when she was 36 had shown a pineal cyst, no other relevant abnormalities were discovered on routine physical examination or laboratory testing. Medical history was remarkable only for her having undergone a complete hysterectomy at the age of 41 after complications from uterine fibroidectomy. There was no history of affective or psychotic disorders.

Over a six week period in our inpatient unit the patient was tapered off benzodiazepines over four weeks and then remained medication free for another two weeks. She showed occasional irritability that was attributed to benzodiazepine withdrawal. During this period the patient was allowed to regulate her circadian exposure to light and dark and to sleep when she wished. Although her sleep was irregular from night to night, she would go to sleep between 0400 and 0830 each morning and sleep until 1000 to 1300.

At the conclusion of this interval, a 24 hour constant routine procedure was undertaken whereby the patient was awake, in virtual darkness (<1 lux), and ate small isocaloric meals every two hours. She was kept awake by engaging her in conversation and sedentary games. Blood samples were obtained via an indwelling intravenous catheter every 30 minutes (1700–1700). Plasma melatonin was measured by StockGrand Ltd (Department of Biochemistry, University of Surrey, UK) with a radioimmunoassay. Rectal temperature was monitored continuously throughout the procedure.

The patient's plasma melatonin rhythm (figure), peaking at 0830, was remarkable particularly for its delayed phase position compared with that typically seen in normal subjects, which peaks in the middle of the night. Rectal temperature exhibited a similarly delayed profile with the nocturnal temperature minimum occurring between about 0500 and 1230.

The delayed timing of the plasma melatonin peak and the rectal temperature minimum provide preliminary evidence that a biological abnormality may be present in the delayed sleep phase syndrome and that the biological dysregulation matches the clinical features of the syndrome. Although it is theoretically possible that our plasma melatonin results differed from those of Alvarez *et al*[1] because their sample consisted mostly of men and our patient was a woman, we have no reason to think that the sex difference might have accounted for the different melatonin profiles. Rather, we suspect that we were able to identify a phase shift in the melatonin profile because its underlying rhythm was unmasked by the 24 hour dim light conditions. Our finding of a similar delay in the circadian temperature rhythm confirms a previous report by Guilleminault *et al*.[4] It is noteworthy that phase advancement of the circadian rhythm of body temperature has been associated with successful treatment of the delayed sleep phase syndrome.[5]

If this report of delayed plasma melatonin and body temperature rhythms in the delayed sleep phase syndrome is replicated in a large sample of patients, it will provide further evidence that plasma melatonin and body temperature rhythms can serve as reliable markers of phase setting of the human body clock that regulates sleep. The establishment of a biological abnormality in this disorder might also provide some solace to those with the disorder, who until now, might have been told that their sleep-wake disorder was psychological in origin. It will also provide biological markers for the diagnosis and progress of treatment of the syndrome.

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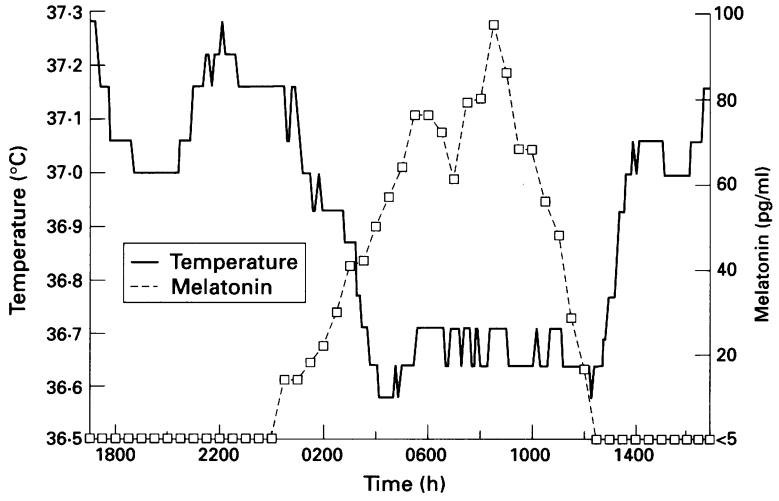

Twenty four hour profile of body temperature and plasma melatonin in a patient with the delayed sleep phase syndrome.

REM sleep behaviour disorder as the presenting symptom of multiple system atrophy

Sleep disturbances are often encountered during the course of multiple system atrophy.[1] The most common features are upper airway dysfunction with snoring and laryngeal stridor and disordered central ventilation with apnoea.[1–3] Other types of sleep disturbance such as rapid eye movement (REM) sleep behaviour disorder (RBD) have also been occasionally reported,[1 2] preceding other signs of the condition in one case.[4] REM sleep behaviour disorder is characterised by the occurrence of intense dream-like motor and verbal behavioural activity during REM sleep, the first often violent and potentially injurious.[5] We report two new cases in whom REM sleep behaviour disorder preceded other symptoms or signs of the disease, to draw attention to

this unusual presentation of multiple system atrophy.

Patient 1 was a man who initially developed a sleep disorder at the age of 57. During sleep, he began to talk or even shout in association with violent muscle jerks such as flinging his arms or lifting himself off the pillow. On several occasions he abruptly got out of bed and injured himself by colliding with furniture. His spouse had sustained several injuries including one apparent attempt at strangulation. These violent attacks lasted for a few minutes and occurred between midnight and 3 00 am. They could be aborted by forceful wakening. Two to three years later, the patient progressively developed a full picture of multiple system atrophy of striatonigral degeneration type with predominantly right sided akinetic rigid syndrome, unresponsive to levodopa, and subsequent impairment of postural reflexes, pyramidal signs, dysarthria and hoarseness, dysphagia, urinary incontinence and retention, impotence, postural hypotension with syncope, and a peripheral sensorimotor neuropathy. The violent behavioural episodes improved, but the nocturnal speech production persisted and snoring and episodes of stridor appeared. Electromyography showed denervation of the external urethral sphincter typically found in multiple system atrophy.[6] Polysomnography with video showed stage 1 and 2 sleep with little deep non-REM sleep and one episode of REM sleep. During light sleep, there were episodes of bilateral fragmentary myoclonic twitches of arms, hands, and thumbs followed by widespread alpha activity for about 30 seconds. During REM sleep, there was atonia on segmental EMG apart from one episode of a sudden flinging movement of both arms with a related increase in EMG activity. No epileptic features were recorded during the episode. None of the other nocturnal behaviours described at the beginning of the disease were recorded on this occasion. There were no apnoeic episodes and no dips in oxygen saturation.

Patient 2 was a man who developed restless and disrupted sleep at the age of 42. He often shouted intelligibly, and sometimes lectured or reprimanded people. The patient was aware of this and said that it was in the context of dreaming. Periodically he would jump out of bed, shake or growl in a stereotyped fashion, or flail his arms. Once he dived out of bed in a rugby tackle, believing he was actually tackling someone. Such episodes occurred at around 5 00 am rather than soon after going to bed, from once a fortnight to twice a week. Episodes of snoring were also noticed. Two to three years later he progressively developed impaired coordination, slurred speech, impotence, and intermittent postural faintness. A full picture of multiple system atrophy of the olivopontocerebellar atrophy type then developed with prominent cerebellar, pyramidal, and dysautonomic signs and symptoms, and mild parkinsonian features. His nights were then predominantly affected by snoring and episodes of stridor. At that time, five years after the onset of nocturnal problems, a sleep study recorded a normal sleep architecture with no excessive movements. No epileptic features or apnoeic periods were recorded, but the patient made "squeaking" noises on inspiration. The baseline saturation was 93% with minor dips throughout the study. Urethral sphincter EMG was again abnormal,[6] and brain MRI showed moderate cerebellar atrophy.

The two patients described developed clinically probable multiple system atrophy of striatonigral degeneration (case 1) and olivopontocerebellar atrophy (case 2) types.[7] In both cases, pronounced sleep disturbances were the first recorded complaint, preceding the onset of the first motor or autonomic symptoms by two to three years. Such sleep disorders, with a history of violent and potentially harmful behaviour and reported vivid dream mentation appropriate to the observed action, are typical of REM sleep behaviour disorder.[5] The disorder was subsequently documented by the recording of a less severe episode in patient 1 during a sleep telemetry study.

Chronic REM sleep behaviour disorder is often reported to be idiopathic[5] and could coincidentally have appeared in these two cases. Beyond the temporal association, however, there are other reasons to believe that REM sleep behaviour disorder was the first manifestation of multiple system atrophy in those patients. Thus REM sleep behaviour disorder has also previously been described during the course of,[1 2] or before the onset of, multiple system atrophy[4] and in familial olivopontocerebellar atrophy, the pathology of which bears some similarity to that of multiple system atrophy.[8] It has also been described in idiopathic Parkinson's disease, occurring late in the disease, but occasionally preceding other symptoms.[5 9] REM sleep behaviour disorder is thought to originate from a dysfunction in pontine structures generating REM sleep muscle atonia.[5] Dream acting behaviour and disappearance of REM sleep muscle atonia have been documented after experimental pontine lesions,[5 8] and pontine lesions are almost always found in both striatonigral degeneration and olivopontocerebellar atrophy variants of multiple system atrophy, with a more restricted involvement of the locus ceruleus in idiopathic Parkinson's disease.[10] It is therefore likely that REM sleep behaviour disorder was the first manifestation of pontine involvement due to multiple system atrophy in our two patients, and has to be added to the growing list of unusual clinical presentations of multiple system atrophy of which physicians should be aware.[7] These two cases also underline the fact that REM sleep behaviour disorder is not always idiopathic, but can instead herald the onset of a major neurodegenerative disorder.[4 5]

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Crying seizures after cerebral infarction

Ictal crying is a relatively rare epileptic condition.[1 3] There have been 11 such cases reported before 1993. Recently seven more cases were reported by Luciano *et al.*[3] The aetiology of the crying seizures in these patients was attributed to tumour, vascular malformations, or mesial temporal sclerosis. There have been no previous case reports of ictal crying after cerebral infarction. We report a case of crying seizures in a patient after cerebral infarction with a seizure focus in the right temporal region.

Three weeks after an inferior wall myocardial infarction, a 66 year old right handed man developed dizziness and a left hemiparesis that resolved over a five day period. He was placed on aspirin (325 mg three times daily). The patient did well until two years later when he awoke with a left hemiparesis. There was no sensory loss or ataxia. Carotid doppler imaging, transthoracic echocardiography, and cardiac monitoring were unremarkable. Brain MRI showed multiple focal ischaemic changes in the white matter, most notably in the posterior limb of the right internal capsule, and mild diffuse cerebral atrophy. The patient was placed on ticlopidine (250 mg twice daily).

The patient did well until seven months later when he began exhibiting unusual behaviour including inappropriate speech, episodes in which he would suddenly stop talking and stare, and episodes of eye deviation to the left. On admission to hospital he was seen to exhibit repeated episodes of deviation of the head and eyes to the left during which time he would begin crying. During these crying episodes he remained alert, answered questions appropriately, and denied any subjective experience of sadness or depression. Electroencephalography performed during these episodes showed ictal discharges occurring repeatedly over the